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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/751,346	01/02/2004	Ron S. Isracli	41426-FA-PCT-US/JPW/CY	7618

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EXAMINER	
YAO, LEI	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 08/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/751,346	ISRAELI ET AL.	
	Examiner	Art Unit	
	Lei Yao, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21,23-25 and 27-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21,23-25 and 27-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/29/04, 9/25/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Amendment filed on 5/12/06 in response to the previous Non-Final Office Action (11/9/05) is acknowledged and has been entered.

Claims 1-20, 22, 26 and 22-58 have been cancelled. Claims 21, 23, 25, 30, 31 have been amended. Claims 21, 23-25, 27-31 are pending and under consideration.

The text of those sections of Title 35, U.S.Code not included in this action can be found in the prior Office Action.

The following office action contains NEW GROUNDS of rejection based on the newly amended claims to a method comprising providing an antibody to outer membrane domain of prostate specific membrane antigen.

Information Disclosure Statement

The information disclosure statement (s) (IDS) submitted on 3/29/04, 12/10/04, 9/12/05, 4/12/06, 6/9/06 are/is considered by the examiner and initialed copies of the PTO-1449 are enclosed.

Rejections Withdrawn

1. The rejection of claims 21, 23-24, 27-31 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody for a prostate specific membrane antigen (PSM) does not reasonably provide enablement for other biological agent is withdrawn because Applicants have amended the claim by replacing biological agent with an antibody. However, newly amended claims are rejected under 35 U.S.C. 112, first paragraph-written description, since specification neither teach the method of killing or eliminating the prostate cancer cells nor teach an antibody used in the method, which specifically binds to outer membrane domain of prostate specific membrane antigen (see below for the details).

2. The rejectiona of claims 21-22, 25 and 27-30 under 35 U.S.C. 102(b) as being anticipated by Brinkmann et al., (PNAS, vol 90, page 547-551, March, 1993) and Claims 21-25 and 27-31 under 35 U.S.C. 102(b) as being anticipated by Chu et al., (US Patent, 4939240, July 1990) or Horoszewicz et al.,

(US Patent, 5162504, Nov, 1992) are withdrawn in view of the amendments to the claims and Applicants' argument.

Response to Arguments

Declaration

Requirement of new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required is maintained for the reasons of record in the prior Office Action 4/25/05.

The response states that Applicants will file a new declaration if necessary, once allowable subject matter is defined. Therefore, the requirement is maintained at this time and states again as the following:

> The oath or declaration is defective because:
>
> The applicants listed in the newly amended specification on page 1 indicating priority of should be in the declaration. A new declaration is required in correlation with the amended specification.

The following is a New Ground of rejection

Priority

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Acknowledgement is made of applicant's claims to an earlier effective filing date PCT/US96/024224 filed on 2/23/1996. Claims 21, 23-25, 27-31, as filed on 1/2/04 and amended on 5/12/06, are drawn to a method of ablating, killing, or eliminating a normal or prostate cancer cells comprising binding an antibody to outer membrane domain of PSMA or antibody bound to a substance effective to kill the cells. Upon review of specification of the applications, it is noted that the PCT/US96/024224 as filed although state, on paragraph 165, "*therapeutic agent comprising antibodies or*

ligand(s) directed against PSM antigen and a cytotoxic agent conjugated thereto or antibodies linked enzymes which activate prodrug to kill the tumor, the cytotoxic agent may either be a radioisotope or toxin" does not provide adequate **support** for the method of ablating, killing, or eliminating a normal or prostate cancer cells comprising binding an antibody to outer membrane domain of PSMA. Therefore, the claims 21, 23-25, 27-31, will have current filing date 1/2/2004.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21, 23-25, 27-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 21, 23-25, 27-31 are vague and indefinite because it is not clear how the cells are killed, ablated or eliminated by an antibody in the amended claim 21. The original claims comprising a biological agent is broadly interpreted as an agent comprising binding portion and killing portion. However, instant claims are amended by replacing biological agent with an antibody. Thus, it is not clear how the antibody alone bind to surface of the cells and kill cells or under condition effective to kill cells. It is also not clear how antibody is bound to a substance effective to kill, ablate or eliminate cells in claim 27. It is not clear that the substance is conjugated to antibody or not. Claims also render the dependent claims indefinite.

Rejection under 35 U.S.C. 112 1st

As drawn to new matter

Claims 21 and 23-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s),

at the time the application was filed, had possession of the claimed invention.

It is noted that the claims 21, 23-25 as newly amended claims recite " eliminating ...epithelial cells comprising an antibody which binds to an outer membrane domain of prostate specific membrane antigen and contacting said cell with antibody under conditions effective to permit both binding of the antibody to the outer membrane domain of the prostate specific membrane antigen and .... eliminating said cells", which is not supported by instant specification. Instant specification as filed, although provide teaches that antibodies against PSM coupled with a cytotoxic agent will be useful to eliminate prostate cancer cells (page 68, line 16-24) does not provide sufficient support for the instant claims reciting eliminating prostate cancer cell or epithelial cells by an antibody only.

As drawn to written description

Claims 21, 23-25, 27-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims encompass a method of killing, ablating, or eliminating prostate cells comprising an antibody binding to outer member domain of PSMA and under condition effective to permit both binding of the antibody to the outer membrane domain of the prostate specific membrane antigen and ablating, killing, or eliminating the cells, wherein the antibody also is bound to substance comprising a toxin effective to kill or eliminate said cells.

The specification on paragraph 244-245, teaches a computer predicted specific membrane-spanning domain of PSMA and states this data enables prediction of inner and outer membrane domains of the PSM antigen which aids in designing antibodies for uses in targeting and imaging prostate cancer. However, the specification neither discloses any of such antibodies which specifically bind to outer membrane domain of the this protein nor any method using such antibody or any antibody bound to a toxin binding to the surface of the prostate cells and kill, or eliminates the cell due to the binding of antibody to outer membrane domain.

While the specification discloses a starting point for making antibodies that may bind to the outer membrane of PSMA protein on the prostate cell, the disclosure does not set forth sufficient procedures that will necessarily lead to kill, ablate, or eliminate the prostate cell with such antibody or antibody bound to a substance. The application does no more than describe the desired function of the claimed antibodies encompassed by the claimed invention and does not contain sufficient information by which a person of ordinary skill in the art would understand that the inventors possessed the claimed invention.

The claimed methods depend upon computer predicted protein sequence of PSMA to design antibodies that specifically bind to the outer membrane of the protein on the prostate cancer cells and using this antibody to binding to surface of the cell and further kill or eliminate the cells. Without such antibodies, which have been tested for certain of binding, the skilled artisan can not practice the claimed method for killing or eliminating the prostate cells. It means little to invent a method if one does not have possession of the antibodies that is (are) essential to practice the method. Without possession of the antibodies, the claimed endpoints are illusory and there is no meaningful possession of the method.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. The claimed methods depend upon computer predicted protein sequence of PSMA to design antibodies that specifically bind to the outer membrane of the protein on the prostate cancer cells and using this antibody to binding to surface of the cell and further kill or eliminate the cells. Without such antibodies, which have been tested for certain of binding, the skilled artisan cannot practice the claimed method of treatment. It means little to invent a method if one does not have possession of the antibodies that is (are) essential to

practice the method. Without possession of the antibodies, the claimed endpoints are illusory and there is no meaningful possession of the method.

Applicant has been reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 1115).

Applicant has been directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, & 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001. Also, see MPEP 2163.

As drawn to enablement

Claims 21 and 23-25, 30-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement antibody alone binding to an outer membrane domain of prostate cancer cell to ablate, kill, or eliminate prostate cancer cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factor considered when determining if the disclosure satisfies the enablement requirement and whether any is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of necessary experimentation claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re wands,* 858 F.2d 731, 737.8 USPQ2d 1400, 1404 (Fed. Cir.1988).

The set of claims is drawn to a method of killing cells comprising an antibody binding to outer member domain of PSMA and contact cells under condition effective to permit both binding of the antibody to the outer membrane domain of the prostate specific membrane antigen and ablating, killing, or eliminating the cells.

The specification teaches that antibodies against PSM coupled with a cytotoxic agent will be useful to eliminate prostate cancer cells (page 68, line 16-24). The specification also teaches a therapeutic agent comprising antibodies or ligand(s) directed against PSM antigen and a cytotoxic agent

conjugated thereto or antibodies linked enzymes, which activate prodrug to kill the tumor and the cytotoxic agent may be a toxin (page 35, line 36). The specification on paragraph 244-245, also teaches a computer predicted specific membrane-spanning domain of PSMA and states this data enables prediction of inner and outer membrane domains of the PSM antigen which aids in designing antibodies for uses in targeting and imaging prostate cancer. However, the specification neither disclose any of such antibodies for outer membrane domain of this protein nor any antibody alone binding to the surface of the cells and kill, or eliminates the cell due to the binding. The specification does not provide any method to ablate or kill cancerous prostate epithelial cells by antibody binding or a working example, which enables any antibody alone or under the conditions effective to permit both binding or kill the cancerous prostate epithelial cells. Therefore, one skilled in the art would not know how to use the claimed method based on the teachings in the prior art or instant specification.

In view of the lack of guidance, lack of examples, and lack of predictability associated with regard to the activity of claimed method of abating or killing cancerous prostate cells by antibody binding to the outer membrane domain of the PSM antigen on the cell, one skilled in the art would be forced into under experimentation in order to practice the broadly claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 21 and 23-25, 30-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murphy et al., (prostate vol 28, page 266-271, 1996) in view of Horoszewicz et al., (US Patent, 5162504, Nov, 1992) and Horoszewicz et al., (Anticancer Res, vol 7, page 927-35, 1987).

Murphy et al., teach antibody 3F5.4G6, which reacts with the extracellular domain (outer membrane) of PSMA (abstract).

Murphy do not teach a method of ablating, killing, or eliminating the prostate cancer cells by antibody or antibody conjugate to a toxin.

Horoszewicz et al., disclose a method of treating prostate cancer with prostate antigen specific antibody conjugated with a toxin (column 7, line 25-30). Horoszewicz et al., also disclose that the antibody to prostate antigen with a pharmaceutical carrier is used to treat human prostate carcinoma patient in conjunction with a toxin either non-covalent or covalent linkages (column 11-12). Horoszewicz et al., further disclose that conjugated antibodies can be administered to patients to achieve enhance tumoricidal effects through the cytotoxic action (column 13, line 7-13). Horoszewicz et al., disclose antibody 9H10-A4H, which only recognizes the surface of prostate cancer cells, LNCap (abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to use the method to kill, ablate, or eliminate the prostate cells comprising providing antibody binding to an outer membrane domain of prostate specific membrane antigen and toxin to eliminate or kill the cells. One of ordinary skill in the art would have been motivated with a reasonable expectation of success to apply the antibodies taught by Murphy et al., to Horoszewicz's method to enhance the prostate cancer treatment by selectively binding the antibody-conjugate to the surface of the membrane of the prostate cancer cells. Because Murphy et al., have shown the antibodies specifically bind to the extracellular domain (outer membrane domain) of prostate specific membrane antigen and Horoszewicz et al., have taught the method of treating prostate cancer cells by antibody-toxin conjugate, one of ordinary skill in the art would have been motivated with a reasonable expectation of success to kill or eliminate the cancer cells with the method.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Tino et al., (Hybridoma, vol 19, page 249-257, 2000) teach antibody, iG9, 3C6, 4D4,which recognize an epitope within the extracellular domain of PSMA. Flow cytometric experiment indicate strong specifically binding to live LNCaP cell by the antibodies. Tino et al., do not teach a method of killing or eliminating prostate cancer cells with the antibodies.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-4.30pm Monday to Friday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lei Yao, Ph.D.
Examiner
Art Unit 1642

LY

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER